UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
ADDRESS: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
WWW.USPTO.GOV

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/903,943	07/11/2001	Avi Ashkenazi	10466-88	1367

30313 7590 10/01/2002

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/903,943	ASHKENAZI ET AL
Examiner	**Art Unit**
Claire M. Kaufman	1646

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *11 July 2001* .

2a)[ ] This action is **FINAL**. 2b)[X] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *39-44* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[·] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[·] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[X] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

DETAILED ACTION

The preliminary amendment filed 07/11/01 and 8/27/02 have been entered.

Specification

The disclosure is objected to because of the following informalities: on page 202, line 37, "Pro317" should be "PRO317".

Additionally, Applicants are advised that the ATCC has moved from Rockville, MD to Manassas, VA, effective March 23, 1998. The correct address is now:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

The specification should be amended to reflect the correct address for the ATCC. See p. 250, lines 1-2.

Appropriate correction is required.

Sequences

The CRF submitted 01/17/02 has been entered with the following correction made by the USPTO STIC staff: for SEQ ID NO:173, a correction to a nucleic acid number at the end of a nucleic acid line has been made. Notice of this correction is provided for Applicant's information, and no action by Applicant is necessary.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39, 44 and dependent claims 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39 and 44 are indefinite because claim 39 recites "binds" and claim 44 recites "specifically binds". Absent a definition of "specific binding" it is not clear what the difference

between the two claims is and what each claim is meant to encompass, given that antibody binding is determined by the variable regions structure and is a "specific" event.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-44 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to an antibody that binds the polypeptide consisting of the sequence of SEQ ID NO:339 (PRO339). In the instant specification, it is stated that PRO339 has homology to fringe, a protein involved in development (p. 34, first paragraph). The level of homology is not disclosed. It is also stated that PRO339 has homology to *C. elegans* proteins and collagen-like polymer sequences. The level of homology is not disclosed in the specification. Sequence search results attached show that there is no more than 2.8% identity between SEQ ID NO:339 and prior art fringe proteins (see attached). For *C. elegans* proteins, no more than 15.5% identity was found (see attached), however, the function of the *C. elegans* protein was unknown. No identity between SEQ ID NO:339 and collagen-like polymers could be identified by the examiner. On the basis of homology, it is suggested in the specification that "PRO339 may be involved in development and tissue growth." (p. 191, lines 11-13) How PRO339 is involved in development or tissue growth is not disclosed. Nor does the prior art provide guidance to allow the skilled artisan to use the claimed polypeptides. None of the sequences sharing sequence identity have a specific or substantial utility. Fringe as discussed by Fleming et al. (*ibid.*) is shown to interact with serrate in drosophila. Wu et al. (Curr. Opin. Neurobiol. 1999 Oct., 9(5):537) say (abstract), "In vertebrates, fringe genes play roles in the formation of apical ectodermal ridge, the dorsal/ventral border in the limb bud, and in the development of somatic borders.....Genetic evidences suggest that Fringe protein functions by modulating the Notch signaling pathway, perhaps through differential regulation of Notch activation by different ligands; however, the mechanism underlying Fringe function remains to be investigated." The

instant specification does not assert any specific functions particular to fringe that might be supported by the prior art. Even it there was a known specific and substantial function of *C. elegans* proteins, fringe proteins or collagen-like polymers, and if such function was disclosed in the specification, the low sequence identity shared between those proteins or polymers and SEQ ID NO:339 would not be sufficient to support any common function because of the lack of function/structure relationship within on of the families that would make it more likely than not that PRO339 possessed any one specific and substantial utility of the prior art proteins. If the antigen does not have utility, the antibody that binds that antigen likewise does not have utility.

The specification asserts another utility for PRO339 (p. 235, lines 2-3): that it is "likely associated with tumor formation and/or growth". This assertion is based on gene amplification expression experiments in colon and lung tumor cell lines and primary cell cultures (p. 225 and 230-235). From Table 9 it appears there was approximately 2-3 fold amplification (about 1 PCR cycle) in 8 or 17 lung tumor primary cell cultures. There is no specific information on what type of the normal tissue was used as a control and how many normals there were. A single normal sample is not sufficient for basing relative levels of many other samples. Even *if* the data demonstrated a slight increase in copy number of PRO339 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO339 can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO339 is overexpressed in any cancer to the extent that it or an antibody that binds to it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

Because it is not know specifically what the functional properties of the polypeptide to which the claimed polypeptide are, the claimed invention is not supported by a specific or well established utility.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The specification provides little beyond structural data and potential activities of the PRO339 polypeptide without guidance about which specific activities one could reasonably expect the polypeptide or encoding nucleic acid to possess as discussed above. Therefore, it would require undue experimentation to use the claimed invention.

35 U.S.C. §§ 102 and 103

The following rejections under 35 U.S.C. §§ 102 and 103 are made under the assumption that the effective filing date for the instantly claimed invention is 07/11/2001, which is the actual filing date of the instant application. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. §120 from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the new claimed invention. Because the instant application does *not* meet the requirements of 35 U.S.C. § 112, first paragraph, for the reasons given above and it is a continuing application of Serial Number 09/665,350, the prior application also does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39-44 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/63088.

WO 99/63088 teaches antibodies to PRO1281 (Figure 233), including monoclonal, humanized and labeled antibodies and antibody fragments (p. 365, line 15, through p. 373, line 25) that would be reasonably expected to bind the polypeptide with the sequence of SEQ ID NO:339 of the instant application because the proteins share large regions of high identity (see attached "Sequence Comparison-WO 99/63088").

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Sibson et al. (WO 94/01548) and Godowski et al. (US Patent 6,030,831).

GenBank Accession No. BAA92640 provides a written description of the polypeptide shown in SEQ ID NO:339 (see attached "Sequence Comparison-GenBank"). GenBank Accession No. BAA92640 does not teach an antibody that binds the polypeptide

Sibson et al. teach the desirability of expressing nucleic acids encoding proteins or fragments of proteins. It is stated (p. 10, line 38) that "Partial or full length cDNAs have great utility once expressed." And (p. 11, lines 9-10), "The proteins thus-expressed can be screened for activities of therapeutic or commercial value." It is taught (. 11, line 17) that "Useful

antibodies can be raised against the expressed proteins." Monoclonal antibodies are also taught (p. 11, last sentence). Numerous generally applicable uses for antibodies are discussed including *in situ* localization of the encoded protein or fragment (p. 21, first paragraph). Methods of antibody production described by Sibson et al. were old and well known in the art (*e.g.*, p. 11, lines 20-22).

Godowski et al. teach general methods of producing and using antibodies including monoclonals, fragments, labeled and humanized antibodies (col. 13, lines 47, through col. 14, line 32, col. 15, lines 38-48, and col. 17, lines 18-36) to secreted proteins (related to TIE ligands).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an antibody, including an labeled, humanized or monoclonal antibody or antibody fragment to the polypeptide of GenBank Accession No. BAA92640 because Sibson outlines the uses, advantages and general methods of making antibodies to proteins encoded by expressed nucleic acids and Godowski et al. teach a variety of antibody types and methods of making and using them. One would have been motivated to make such antibodies to us in protein localization, for example.

Claims 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Applicants' Admission on p. 34, lines 5-6 and Fleming et al. (Dev., 124:2973-81, 1997) and Godowski et al. (US Patent 6,030,831).

The disclosure of GenBank Accession No. BAA92640 is discussed above. GenBank Accession No. BAA92640 does not teach an antibody that binds the polypeptide

Applicants admit (p. 34, lines 5-6) in the instant specification that disclosed PRO339 polypeptide has homology to fringe. Therefore, the polypeptide of GenBank Accession No. BAA92640 necessarily shares homology with fringe.

Fleming et al. teach that fringe is a secreted polypeptide, necessarily lacking an associated signal peptide when secreted (Fleming et al, , p.2974, second sentence of second paragraph).

Godowski et al. teach general methods of producing and using antibodies including monoclonals, fragments, labeled and humanized antibodies (col. 13, lines 47, through col. 14,

line 32, col. 15, lines 38-48, and col. 17, lines 18-36) to secreted proteins (related to TIE ligands). The uses include competitive binding assays to determine binding properties of the protein with known or suspected binding partners.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an antibody, including an labeled, humanized or monoclonal antibody or antibody fragment to the polypeptide of GenBank Accession No. BAA92640 because Fleming et al. teach an active secreted fringe protein that Applicants admit is related to the protein with the sequence of GenBank Accession No. BAA92640. For the reasons set forth in Godowski et al., one would have been in possession of the necessary routine methods to and motivation for making such an antibody, for example to identify and characterize proteins that naturally bound the antigen.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Nagase et al. (DNA Res. 7 :65-73, 2000) teach the isolation and analysis of GenBank Accession No. BAA92640 (K1AAA1402 protein). WO200153312 teaches polypeptide SEQ ID NO :2926 as shown on the summary sheet provided and labeled "WO200153312 Comparison" which is identical to SEQ ID NO:339 of the instant application. This publication has not been furnished in whole due to the length of over 10,000 pages. WO200153312 could serve as a reference under 102(e) and would be cumulative with the references relied on above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

September 27, 2002